a methanolic solution of diazomethane. The reaction mixture was chromatographed on a column of silica gel. Elution with hexane–ethyl acetate (4:6) provided **4c** (169 mg) and 4-(methylthio)-3-(2′,3′,5′-tri-*O*-acetyl-D-ribofuranosyl)pyridine [**5c** (11 mg, 5%)] as an anomeric mixture. **5c**: MS *m/e* 384 [$(M + 1)^+$·], 323 [$(M - 60)^+$·]; NMR δ 8.90 (d, 1, H-6), 8.47 (s, 1, H-2), 6.96 (d, 1, H-5), 5.50–5.07 (m, 3, H-1′, H-2′, and H-3′), 4.40–4.10 (m, 3, H-4′ and 2 × H-5′), 2.46 (s, 3, CH_3S), 2.12, 2.08, and 2.05 (3 ×) (s, 3, CH_3CO).

Treatment of compound **5c** (24 mg) with $NaOCH_3$ in methanol followed by neutralization with Amberlite IR 120 (H^+) gave an anomeric mixture of pseudonucleosides which after reaction with 2,2-dimethoxypropane gave the corresponding mixture of acetonide derivatives **4d**. Purification of the β isomer was accomplished by silica gel preparative TLC ($CHCl_3$–MeOH, 9:1) to give 3-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-4-(methylthio)pyridine [β-**5d** (12 mg)] as an amorphous solid. β-**5d** ($C_{14}H_{19}NO_4S$): M^+· found 297.1030; UV λ_{max} 264 nm (ϵ 11 000); NMR δ 8.50 (s 1, H-2), 8.39 (d, J = 5.5 Hz, 1, H-6), 7.07 (d, J = 5.5 Hz, 1, H-5), 5.08 (d, J = 4 Hz, 1, H-1′), 4.78 (m, 2, H-2′ and H-3′), 4.13 (m, 1, H-4′), 3.96–3.73 (m, 2, 2 × H-5′), 2.45 (s, 3, CH_3S), 1.63 and 1.36 (2 ×) (s, 3, CH_3).

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Registry No.—1 (R = CH_3), 18438-38-5; **1a**, 51290-79-0; **1b**, 2637-34-5; **1c**, 69493-87-4; **2a**, 69493-88-5; α-**2d**, 69493-89-5; β-**2d**, 69502-45-0; **3a**, 69493-90-9; α-**3d**, 69493-91-0; β-**3d**, 69493-92-1; **4** (R = CH_3), 22581-72-2; **4a**, 51290-78-9; **4b**, 4556-23-4; α-**4c**, 69493-93-2; β-**4c**, 69493-94-3; α-**4d**, 69493-95-4; β-**4d**, 69493-96-5; **5a**, 69493-97-6; α-**5c**, 69493-98-7; β-**5c**, 69493-99-8; β-**5d**, 69494-00-4; **6** (R = ribosyl), 54606-57-4; **6c**, 69494-01-5; **6d**, 69494-02-6; 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose, 28708-32-9.

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(13) The difference in the stereoselective course for the preparation of **2c** and **4c** might be explained by considering that 4-(alkylthio)pyridines are more basic than 2-(alkylthio)pyridines (ΔpK_a).[5] Consequently, under the reaction conditions the pyridinium species derived from **4c** might undergo a nucleophilic substitution involving 4-mercaptopyridine (**4b**) to give the corresponding α-thionucleoside. In support of this view we have observed the formation of a minor amount of **2c** when we treated an anomeric mixture of **4c** with 2-mercapotpyridine (**2b**) in the presence of BF_3:Et_2O in dichloroethane.
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Preparation of α-Substituted β-Alanine Derivatives from 5-Substituted Uracils and Dihydrouracils

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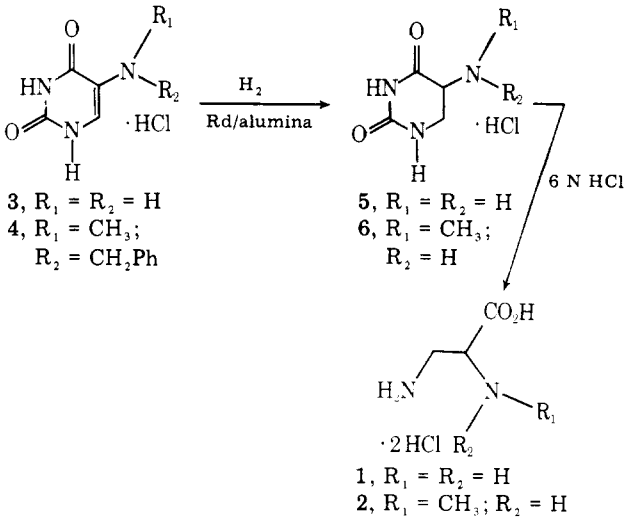
In the course of synthesizing new cyclic analogues of creatine to examine the substrate specificity of the enzyme creatine kinase, we needed reasonable quantities of both 2,3-diaminopropanoic acid (**1**) and 2-(methylamino)-3-aminopropanoic acid (**2**). Compound **1** is available commercially at high cost and can be prepared as the dihydrobromide from 2,3-dibromopropanoic acid and ammonia, but the yield is only 40–50% and high temperatures and pressure are required.[3]

Scheme I



2-(Methylamino)-3-aminopropanoic acid (**2**) was first reported[4] as one of the hydrolysis products of deoxytheobromine (3,7-dimethyl-2-oxo-1,6-dihydropurine).[5] This synthetic procedure, which first requires the reduction of theobromine to deoxytheobromine,[5] suffers from low yields and, in our hands, poor reproducibility.

Martin et al.[6] also report a synthesis of **2**, in this case from the condensation of diethyl (*N*-methyl-*N*-acetylamino)malonate[7] and *N*-(bromomethyl)phthalimide[8] followed by acid-catalyzed hydrolysis of the condensation product. A 30% yield was reported for these final two steps.[6]

An alternative method for the synthesis of compounds **1** and **2** is presented in Scheme I.

Compound **3**, 5-aminouracil, is commercially available, and **4**, 5-(*N*-benzyl-*N*-methylamino)uracil[9] is easily prepared in high yield from commercially available 5-bromouracil. The hydrogenation steps are nearly quantitative for **3** and **4**. The acid-catalyzed hydrolyses of **5** and **6** each give 1 equiv of ammonium chloride as a coproduct along with the dihydrochloride of the corresponding diamino acid. The two products are easily separated by means of ion exchange chromatography on a strongly basic anion exchange resin. The amino acid and chloride ion bind tightly to the column, and the ammonia is eluted with water. The amino acid can then be removed from the column by elution with an acidic solution, e.g., 1.0 N HCl or 1.0 N HCO_2H.

The overall method should be directly applicable to the preparation of a variety of 2-(alkylamino)-3-aminopropanoic acids from other 5-substituted aminouracils, which in turn are easily prepared from 5-bromouracil and the appropriate amine.[9] Also, any 5-substituted uracil derivative in which the 5-substituent is stable to the hydrogenation and acid-catalyzed hydrolysis conditions potentially could be converted to the corresponding α-substituted β-alanine derivative. Some β-substituted β-alanine derivatives have been prepared from their corresponding 6-substituted dihydrouracils in good yields using similar methods to those we describe here, although convenient starting materials are not commercially available and not all of the 6-substituted dihydrouracils examined gave the expected β-alanine derivatives.[10]

We have extended this procedure to obtain reasonably high

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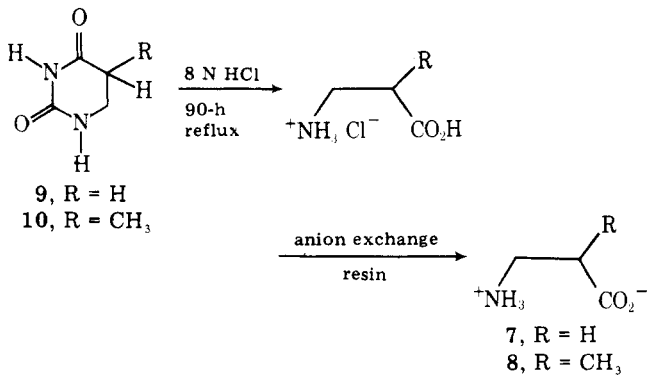
Scheme II



9, R = H
10, R = CH_3

7, R = H
8, R = CH_3

yields (77–87%) of both β-alanine (7) and β-aminoisobutyric acid (8) by the hydrolyses of commercially available dihydrouracil (9) and 5-methyldihydrouracil (10), respectively, as shown in Scheme II. Both 7 and 8 had been previously prepared in 56–65% yield by Zilkha et al.[11] by the hydrogenolysis of the corresponding *N*-benzyl derivatives, which were prepared by the addition of benzylamine to acrylic acid or methacrylic acid, respectively. A number of other less general methods have been reported for the syntheses of β-alanine[12–16] and β-aminoisobutyric acid.[17–21]

Experimental Section

General. Proton NMR spectra were determined on a Varian A-60A spectrometer in D_2O and are reported relative to the internal standard sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS). Melting points are uncorrected, and microanalyses were obtained from the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley, Calif.

β-Alanine (7) from Dihydrouracil (9). Dihydrouracil (9; 3.0 g, 26 mmol; Sigma Chemical Co.) was heated at reflux for 90 h in 105 mL of 8 N HCl. The excess HCl and water were removed in vacuo. After the residual solid was washed with acetone several times, the dry product was heated under reflux with stirring in 100 mL of 2-propanol until the lumps disintegrated. The coproduct, NH_4Cl, was filtered off and washed with 30 mL of hot 2-propanol. The filtrate, on cooling overnight, gave 2.0 g of the crystalline product. By concentrating the filtrate to 10–20 mL and cooling, an additional 0.5 g of the product was obtained (total 2.5 g, 77% yield). On recrystallization from 2-propanol, the product, β-alanine hydrochloride, melted at 122–123 °C (lit.[13] 121–122 °C).

β-Alanine hydrochloride (2.0 g, 16 mmol) was dissolved in 3 mL of water and passed through a column packed with weakly basic anion exchange resin (Bio-Rad AG3-X4A, 20–50 mesh, ^-OH form) containing 20 mL of resin at the rate of 1–2 mL/min with water as eluent. Ninhydrin-positive fractions were pooled and concentrated to dryness in vacuo to give crystalline, hydrochloride-free β-alanine (7) in 93–100% yield. Recrystallization from aqueous ethanol gave analytically pure 7 as white crystals (79–85% recovery), mp 197–198 °C dec (lit.[14] 197–198 °C dec).

β-Aminoisobutyric Acid (8) from 5-Methyldihydrouracil (10). 5-Methyldihydrouracil (10; 4.0 g, 31 mmol; Sigma Chemical Co.) was heated at reflux in 120 mL of 8 N HCl for 90 h. The same procedure as described above for the isolation of β-alanine hydrochloride gave crystalline β-aminoisobutyric acid hydrochloride in 80–87% yield. On recrystallization from 2-propanol, the hydrochloride of 8 melted at 127–129 °C.

By treating the hydrochloride with weakly basic anion exchange resin as described in the preparation of β-alanine, the hydrochloride-free product was obtained in 98–100% yield. The white crystalline product (10), which was recrystallized from 95% ethanol–acetone, melted at 176.5–177.5 °C (lit. 181[11] and 171–172 °C[20]); ^1H NMR δ 1.16 (3 H, d, J = 8 Hz), 2.2–3.1 (3 H, m).

5-Amino-5,6-dihydrouracil Hydrochloride (5). 5-Aminouracil (3; 7.7 g, 60 mmol; Aldrich Chemical Co.) was converted to its hydrochloride salt by treatment with 6 N HCl followed by removal of the excess aqueous acid in vacuo. The pale yellow solid was then suspended in 200 mL of water and hydrogenated (45 psi) in the presence of 1 g of 5% rhodium on powdered alumina (Matheson Coleman and Bell). After the theoretical amount of hydrogen had been absorbed (24 h), the catalyst was separated by filtration and the water was removed in vacuo. The product (5) was purified by recrystallization from ethanol–water to give 9.6 g (97% yield) of colorless crystals, mp 239–241 °C dec.

Anal. Calcd for $C_4H_8ClN_3O_2$: C, 29.02; H, 4.87; Cl, 21.41; N, 25.38. Found: C, 28.93; H, 4.92; Cl, 21.16; N, 25.11.

The ^1H NMR spectrum showed peaks at δ 3.3–4.1 (2 H, multiplet, ABC pattern) and 4.54 (1 H, doublet of doublets, J = 7 and 13 Hz).

2,3-Diaminopropanoic Acid Monohydrochloride (1). 5-Amino-5,6-dihydrouracil hydrochloride (5; 6.0 g, 36 mmol) was heated at reflux for 72 h in 150 mL of 6 N HCl. The aqueous acid was removed at reduced pressure, and the residue was taken up in water several times and concentrated in vacuo to remove residual HCl, leaving the dihydrochloride of 2,3-diaminopropanoic acid and 1 equiv of ammonium chloride. The product was dissolved in 5 mL of water and applied to a 50-g column of Bio-Rad AG-1-X8, 20–50 mesh, ^-OH form, anion exchange resin. The column was eluted with water until the effluent was neutral to pH paper. The diamino acid was then eluted with 1 N HCl as the dihydrochloride salt until the column effluent was no longer ninhydrin-positive. The product, after concentration in vacuo, was dissolved in a minimum amount of warm methanol, and pyridine was added to the solution until the pH rose to a value of about 4. The precipitate was recrystallized from aqueous ethanol to give 4.6 g (90% yield) of 2,3-diaminopropanoic acid monohydrochloride (1), mp 225–226 °C (lit.[22] mp 226–227 °C). The proton NMR was identical with that of the commercially available material.

5,6-Dihydro-5-(methylamino)uracil Hydrochloride (6). 5-(*N*-Methyl-*N*-benzylamino)uracil hydrochloride (4; 4.0 g, 15 mmol) was hydrogenated as in the 3 → 5 conversion to give a quantitative yield of 5,6-dihydro-5-(methylamino)uracil hydrochloride (6, 2.65 g). A sample was recrystallized for elemental analysis from aqueous ethanol, mp 239–240 °C.

Anal. Calcd for $C_5H_{10}N_3O_2Cl$: C, 33.44; H, 5.61; N, 23.40. Found: C, 33.15; H, 5.50; N, 23.13.

The ^1H NMR spectrum showed peaks at δ 2.91 (3 H, singlet) and an ABC pattern at δ 4.53 (J = 6.5 and 12.5 Hz).

2-(Methylamino)-3-aminopropanoic Acid Monohydrochloride (2). 5,6-Dihydro-5-(methylamino)uracil (6; 2 g, 11.1 mmol) was heated at reflux for 72 h in 50 mL of 6 N HCl, after which the aqueous HCl was removed in vacuo. The crude product was separated from the ammonium chloride and converted to the monohydrochloride as in the 5 → 1 conversion. The pH of the resulting methanol solution was adjusted to approximately 5 with pyridine, and the white crystalline solid that formed was collected by filtration to give 1.3 g of product 2 (76% yield). A sample was recrystallized from aqueous ethanol for elemental analysis, mp 200–213 °C dec.

Anal. Calcd for $C_4H_{11}N_2O_2Cl$: C, 31.08; H, 7.17; N, 18.12; Cl, 22.93. Found: C, 31.21; H, 7.17; N, 18.18; Cl, 22.88.

The ^1H NMR spectrum showed peaks at δ 3.85 (3 H, singlet) and an ABC pattern at δ 3.4–4.2 with a doublet of doublets centered at δ 4.0 (J = 5 and 8.5 Hz).

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Registry No.—1, 6018-55-9; 2, 69652-32-0; 3, 69652-31-9; 4, 69686-93-7; 5, 69652-33-1; 6, 69652-34-2; 7, 107-95-9; 7 hydrochloride, 6057-90-5; 8, 144-90-1; 8, hydrochloride, 28267-25-6; 9, 504-07-4; 10, 696-04-8.

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